REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 15-21, 23-27, 33, 48, 49, and 117-128 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully requested.

Claims 80-81, 83-94, 96-106, 108-116 have been rejected under 35 U.S.C. §102(a) as being anticipated by Viardot et al., *Blood* 10(Suppl. 1, part 1):478 (1997). This rejection is obviated by the cancellation of the rejected claims without prejudice to the filing of a continuing application thereon.

Claims 1-14 have been rejected under 35 U.S.C. §102(a) as being anticipated by Mohle et al., *Blood* 91(12):4523-4530 (1998). This rejection is also obviated by the cancellation of rejected claims 1-14 without prejudice to the filing of a continuing application thereon.

Claims 1, 3-5, 10-14, 53-64, and 80-104 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Cancellation without prejudice of the rejected claims obviates this rejection.

Claims 15-27, 33, and 48-49 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Kanz et al., U.S.

Patent 5,541,103 in view of Mohle et al., *Blood* 91(12):4523-4530 (1998).

Kanz discloses the *ex vivo* expansion of peripheral blood progenitor cells that can be administered to cancer patients after chemotherapy. The Mohle secondary reference is cited by the examiner for its disclosure of an *in vitro* transendothelial migration assay and its teaching that $CXCR4^+$ hematopoietic progenitor cells which migrate in response to SDF-1 would have enhanced capability to migrate and home in to the bone marrow and that this would increase their usefulness for transplantation, as set forth in Paper No. 7. The examiner asserts that based on the motivation provided by Mohle for sorting $CXCR4^+$ progenitor cells which transmigrate in response to SDF-1 for use in transplantation in order to increase stem cell homing and migration, it would have been *prima facie* obvious to further purify the stem cells produced by Kanz by using the transmigration assay taught by Mohle. It is the examiner's position that, in view of the successful use of the transmigration assay to isolate $CXCR4^+$ stem cells which migrate in response to SDF-1 by Mohle, the skilled artisan would have had a reasonable expectation of success in using this method to sort stem cells produced by the method of Kanz that migrate in response to SDF-1. This rejection is respectfully traversed.

Assuming for the sake of the present argument that the examiner has established a *prima facie* case of obviousness on the ground that Mohle suggests a method of sorting out $CXCR4^+$ cells from any source, including the expanded $CD34^+$ cells of Kanz, any case of *prima facie* obviousness can be overcome by a showing of unexpected results. See MPEP §716.02(a).

Kanz starts with $CD34^+$ hematopoietic stem cells and simply expands them. The ending material is simply a larger quantity of $CD34^+$ stem cells. Kanz is totally silent about the CXCR4 status of such stem cells. No one of ordinary skill in the art reading Kanz would expect that any characteristics of the cells are being changed by this expansion. Thus, if 25% of the starting cells happen to be $CXCR4^+$, one would expect that 25% of the ending cells would be $CXCR4^+$.

Mohle merely teaches a technique for sorting out $CXCR4^+$ stem cells. There is no reason for anyone of ordinary skill in the art reading Kanz and Mohle to believe that the number of $CXCR4^+$ cells in the ending material of Kanz, which is the starting material of Mohle, would contain any more than the expected average amount of $CXCR4^+$ cells.

However, Examples 3 and 4 of the present specification demonstrate the unexpected finding that the stimulation of $CD34^+$ cells with SCF surprisingly results in increased CXCR4 expression (Fig. 3A) and that the percent of sorted stem cells suitable for

engraftment was unexpectedly increased from about 25% of the population of cells to about 75% (25% migrating $CXCR4^{+}$ stem cells and 50% adhering $CXCR4^{-/low}$ stem cells which can be converted to $CXCR4^{+}$ stem cells).

The unexpected and surprising discovery of the present invention is that a substantial number of $CXCR4^{-/low}$ stem cells can be converted to $CXCR4^{+}$ stem cells. Whether or not this inherently occurs in the process of Kanz is irrelevant, as this is not an anticipation rejection but an obviousness rejection. As stated in *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966), quoted with approval in *In re Shetty*, 195 USPQ 753, 757 (CCPA 1977):

> As we pointed out in *In re Adams*, 53 CCPA 996 356 F.2d 998, 148 USPQ 742 [(1966)], the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.

As the increased percentage of $CXCR4^{+}$ stem cells is quite unexpected and part of the invention as a whole, any *prima facie* case of obviousness established by the examiner has been rebutted by the data in the present specification. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Another difference between the process of the present invention and that of Kanz is that the *ex vivo* expansion in Kanz is accomplished by incubating the peripheral blood progenitor

cell with growth factors for about 3-4 weeks, e.g., up to 28 days in Kanz's Example 4 and for 21 days in Kanz's Example 5, thus achieving a 20-fold to 100-fold expansion. New claims 123-126 have now been added, which specify that the period of stimulation is only up to 5 days, preferably about 1-2 days. It would not be even *prima facie* obviousness from any reading of Kanz and Mohle that such a short period of stimulation will have any utility whatsoever. Accordingly, new claims 123-126 are patentable in their own right.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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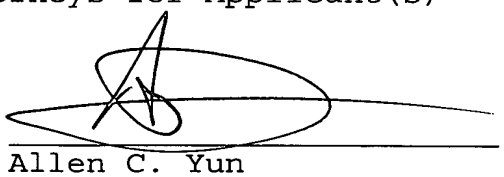
By 
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